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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,371	01/25/2005	William Richard Cross	15892.9	1386

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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,371	CROSS ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15-26 and 29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15-26 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 06/17/2010.

Claims 13, 20, 21, 24, 31, 34 and 35 have been amended. No claims have been newly added or newly canceled.

Claims 13, 15-26, 29-35 are currently pending and have been examined on the merits.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 15-19, 21, 23-26, 29-35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cross et al. (Biochemical Society Transactions 2001, from IDS) in view of Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001).

Amended claim 13 is drawn to a method of production of stratified, terminally-differentiated human urothelium in which urothelial cells, isolated from the human body and propagated by culture in serum-free medium, are transferred to a first nutrient differentiation medium containing serum and then redispersed by passage before being

added to a fresh second nutrient differentiation medium containing serum to form the urothelium.

Dependent claims include wherein the serum is bovine serum, wherein the bovine serum is adult or fetal, the concentration range of the components of the serum, wherein the nutrient medium is KSFM, and the urothelium produced by the method of claim 13.

Amended claim 24 is drawn to a method of production of stratified, differentiated human urothelium comprising: serial culture of human urothelial cells in a serum-free medium; replacing the serum-free medium with a first differentiation medium that includes whole serum; maintaining the cells to form a cell culture having aggregated cells, dispersing and disaggregating the cells into a fresh second differentiation medium that includes whole serum and culturing the cells so as to form stratified, terminally-differentiated human urothelium.

Dependent claims include wherein the aggregated cells are at least partially confluent and approach confluency, wherein the serum is between about 1% and 30% and 4% and 6% of the medium, wherein the first, second differentiation culture medium is one of MCDB-153, KSFM, or derived thereof, wherein the first, second differentiation culture medium is supplemented by EGF, BPE, or CT, and increasing the calcium concentration in the second differentiation cell culture medium (this is interpreted as requiring that the calcium concentration be increased compared to any prior media used).

Amended claim 34 is drawn to a method of production of stratified, differentiated human urothelium, the method comprising culture of human urothelial cells in a serum-free nutrient medium; replacement of the serum-free nutrient medium with a first differentiation culture medium that includes at least 5% whole serum, maintaining the cells in the first differentiation medium to form a secondary culture having aggregated cells; dispersing and disaggregating the cells into a second differentiation culture medium that includes at least 5% whole serum and culturing the cells and increasing the calcium concentration of the second differentiation medium so as to form the stratified, terminally-differentiated human urothelium.

This is interpreted as requiring that the differentiation media used after the first and second differentiation media have an increased calcium concentration compared to any prior media used.

Aggregated cells are interpreted to mean at least two or more cells that are touching each other.

Amended claim 35 is dependent upon claim 34 and further includes determining the urothelial cells cultured in the second differentiation culture medium to have stratified layers of terminally-differentiated human urothelium.

Cross et al. teach that normal human urothelial cells propagated in serum-free medium exhibited a low transepithelial electrical resistance and a high FITC-Dextran permeability. The addition of serum to the culture system resulted in urothelial stratification, intercellular tight junction formation, a high transepithelial electrical resistance, a low FITC-Dextran permeability and the expression of amiloride sensitive

sodium channels. This human *in vitro* urothelial tissue model expresses many of the morphological and functional properties of the *in vivo* system (abstract).

Cross et al. are silent with regard to the exact media used and the number of cell passages from the establishment of primary cultures to the final product.

Zhang et al. teach that KSFM provides an optimal medium to separate urothelial cells selectively from other types of cells and can be used for an initial culture before subculturing (redispersing) the cells in a serum-supplemented media for long-term cultures (page 428, column 1, paragraph 3). Establishment of primary cultures with a serum free media that contains EGF, BPE and CT is taught (page 419 materials and methods) along with subsequent expansion with different medias containing serum (one with 5% FBS) until passage 2, which would inherently require a second and third culture medium that includes serum (page 422, column 1, paragraph 3-4). The cells are at least partially confluent and approaching confluency and therefore contain cells that are touching each other (aggregated) (page 427, column 1).

While Cross is silent with regard to the steps used in their culture system, Zhang demonstrates what is well known in the art of propagating urothelial cells which is that the culturing of urothelial cells to produce a stratified differentiated model requires passaging steps which include steps of redispersal from a serum-containing medium into another (fresh) serum-containing medium.

Therefore, one of ordinary skill in the art would have been motivated to use a serum free media such as KSFM in the establishment of primary urothelial cultures because Zhang et al. teach that KSFM provides an optimal medium to separate

urothelial cells selectively from other types of cells and can be used for an initial culture before subculturing (redispersing) the cells to obtain a pure urothelial cell culture (page 422, column 2). One of ordinary skill in the art would have been motivated to switch to media containing serum for the subsequent passages of urothelial cells because Cross et al. teach that the addition of serum containing media to urothelial cultures yields a human *in vitro* urothelial tissue model expressing many of the morphological and functional properties of the *in vivo* system (abstract). The number of passages required would have been a matter of routine optimization, the artisan of ordinary skill would be motivated to adjust the number of passages depending on the amount of urothelium required for the end product. One of ordinary skill in the art would have been motivated to use bovine serum at about 5% and low increasing levels of calcium because Zhang et al. teach that these are suitable additions and concentrations for the growth of urothelial cells. One of ordinary skill in the art would have had a reasonable expectation of success in using these techniques in the method of Cross et al. because Zhang et al. teach that culture techniques such as these are applicable to other primary tissue culture systems where potential contamination and subsequent overgrowth with fibroblasts remain a problem (page 428, column 2, last paragraph).

One of ordinary skill in the art would have been motivated to combine different media in the method of Cross et al with a reasonable expectation of success because Zhang et al teach that a combination of different media gives better yields than any single medium (page 427, column 1). This would allow for the first differentiation medium to be a different type from the second differentiation medium.

Therefore, the combined teachings of Cross et al. and Zhang et al. render obvious Applicant's invention as claimed.

Claim 16 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Cross et al. (Biochemical Society Transactions 2001, from IDS) in view of Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001) as applied to claims 13, 15-19, 21, 23-26, 29-35 above and further in view of Seijiro et al (US 4,654,304) and Jefferson et al (US 5,380,660).

Claim 16 is drawn to the method of claim 15 wherein the serum is adult or fetal bovine serum.

The combined teachings of Cross et al and Zhang et al render obvious the method as described above, but do not specifically include adult bovine serum.

Seijiro teaches that serum to be used in the cultivation of animal cells or tissues may be derived from any species, although bovine, among others, may be advantageously used for reasons of their ready availability (column 1 lines 64-68). The mammals from which the serum is derived may be at any age, e.g., fetuses, newborns, youngs or adults (column 2 lines 1-2). Clearly adult bovine serum is considered by Seijiro to be a suitable substitute for fetal or newborn bovine serum.

Jefferson et al teach a method of reducing the loss of differentiation functions of cells cultured in culture medium containing serum which includes an inhibitor of cellular differentiation. The method includes treating the serum or serum-containing medium to

remove or inactivate the inhibitor (abstract). The inhibitory activity in adult bovine serum appeared less potent than fetal calf serum (column 4 lines 54-56). Any serum that is capable of promoting cellular longevity in culture, e.g., fetal calf serum or adult bovine serum may be used (column 10 lines 50-52). While hepatocytes are specifically used with the serum –containing medium as an example, the data is suggested as relevant for many types of cells (column 3 lines 35-40). Clearly adult bovine serum is deemed to be an acceptable alternative to fetal calf serum when culturing cells for differentiation purposes.

Therefore, one of ordinary skill in the art would have been motivated to substitute adult bovine serum for fetal or newborn bovine serum in the method of Cross et al because Seijiro teaches that mammals from which the serum is derived may be at any age, e.g., fetuses, newborns, youngs or adults (column 2 lines 1-2). One of ordinary skill in the art would have had a reasonable expectation of success because Seijiro had demonstrated that the adult bovine serum possessed growth promoting substances (column 11 table 4) and because Jefferson et al also teach that adult bovine serum may be substituted for fetal calf serum for long term culture of cells as well.

Therefore, the combined teachings of Cross et al, Zhang et al, Seijiro and Jefferson et al render obvious the invention as claimed.

Claims 20 and 22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cross et al. (Biochemical Society Transactions 2001, from IDS)

in view of Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001) as applied to claims 13, 15-19, 21, 23-26, 29-35 above and further in view of Judd et al (US 6,692,961 B1).

Claim 20 includes wherein the nutrient differentiation medium includes, or is a derivative of, MCDB-153 medium.

Claim 22 includes wherein the nutrient differentiation medium is supplemented by one or more of EGF, BPE, or CT.

The combined teachings of Cross et al and Zhang et al render obvious the invention as described above, but do not teach the use of supplemented MCDB-153 medium.

Judd teaches a defined system for epithelial cell culture and indicates that MCDB-153 (which includes EGF and BPE) is a suitable alternative for KSFM medium (column 5 lines 1-13). Judd also teaches the benefits of adding EGF and/or cholera toxin (CT) to the media as well (column 11 lines 10-40).

Therefore, one of ordinary skill in the art would have been motivated to substitute MCDB-153 medium for KSFM in the method of Cross et al because Judd et al indicate that MCDB-153 is a suitable alternative for KSFM medium (column 5 lines 1-13). One of ordinary skill in the art would have had a reasonable expectation of success because the teachings of Judd et al were drawn to the *in vitro* cultivation of animal epithelial cells.

Therefore, the combined teachings of Cross et al, Zhang et al, and Judd et al render obvious the invention as claimed.

Response to Arguments

Applicant's arguments filed 06/17/2010 have been fully considered but they are not persuasive.

Applicant argues that the Cross reference is not available as prior art because the current invention predates the publication of the Cross reference. Applicant asserts that the 131 declaration of Jennifer Southgate removes the Cross reference as available prior art.

This is not found persuasive because the effective filing date of the current application is 07/28/2003 and therefore the 2001 Cross reference predates this by more than a year making the Cross reference date a 102 (b) type reference. A reference with a 102 (b) date presents a statutory bar which cannot be sworn behind. A 131 declaration can only be used against a reference that has a date that is less than a year before the effective filing date of an application.

Applicant argues that the claimed invention produces unexpected results and is therefore nonobvious over the prior art. Applicant asserts that the Freshney reference teaches against the claimed method for producing stratified terminally differentiated human urothelium.

This is not found persuasive as the Freshney reference does not teach against the claimed method. The Freshney reference was cited in response to Applicant's

arguments and to demonstrate that the term "passaging" was well known in the art and that it inherently included the same steps as cited by Applicant. The Cross reference in view of the Zhang reference demonstrate that Applicant's method as claimed would be obvious to one of ordinary skill in the art.

Applicant asserts that the Declarations provided from Jennifer Southgate include evidence that the combination of the Zhang and Cross references does not teach or suggest Applicant's invention as claimed. Applicant asserts that the Declarations provide evidence of secondary considerations that rebut the alleged obviousness.

The declarations under 37 CFR 1.132 filed 06/17/2010 are insufficient to overcome the rejection of claims 13, 15-19, 21, 23-26, 29-34 based upon the combined teachings of the Cross and Zhang references applied under 35 USC 103 as set forth in the last Office action because: It refer(s) only to the method described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

The Southgate declaration argues that the results of the currently claimed method are surprising and unexpected because:

1) the use of serum as a differentiating factor is non-obvious due to its association with promotion of proliferation and

2) the use of redispersal of cells as part of a differentiation-inducing procedure is non obvious because such procedure: a) is routine to subculture to promote proliferation

and b) does against the established approach of promoting 3D structures for achieving differentiation.

This is not found persuasive because the Cross reference explicitly teaches that serum-supplemented media is responsible for the stratified terminally-differentiated human urothelium and the Zhang reference provides the passaging steps required that are known in the art for the culture of cells as well as the same base media as claimed by Applicant to be supplemented. Cross et al. teach that normal human urothelial cells propagated in serum-free medium exhibited a low transepithelial electrical resistance and a high FITC-Dextran permeability. The addition of serum to the culture system resulted in urothelial stratification, intercellular tight junction formation, a high transepithelial electrical resistance, a low FITC-Dextran permeability and the expression of amiloride sensitive sodium channels (abstract). No where does the reference suggest that the cells should not be redispersed. The term "propagating" is interpreted that the cells are cultured as is known in the prior art and suggested by those of skill in the prior art (such as Zhang). Also the use of serum for differentiating is explicitly taught as well and therefore also considered obvious.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

It is suggested that Applicant amend the claims to include those physical methods steps that distinguish the claimed method from the method described in the Cross reference and the routine passaging of cells that is well known in the prior art.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg